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Toxicity and Carcinogenesis Studies of Tetralin in F344/N Rats and B6C3F1 Mice

(Inhalation Studies)

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NTP Board of Scientific Counselors

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Tetralin

- Tetralin is a liquid that is insoluble in water and soluble in organic solvents
- Used as a solvent for naphthalene, fats, resins, oils, and waxes, as a substitute for turpentine, and as a constituent of motor fuels and lubricants
- Found in the environment as result of combustion and waste discharge
- Humans are exposed to tetralin through dermal contact or inhalation during manufacture or use

Metabolism and Disposition

- Hydroxylation at the nonaromatic portion of the molecule
- Excreted in male rat urine as glucuronic acid or sulfate conjugates
  - Mono alcohols (1-tetralol and 2-tetralol)
  - Hydroxyketones (2-hydroxy-1-tetralone and 4-hydroxy-1-tetralone)
  - Diols (1,4-tetralindiol and 1,2-tetralindiol)

Toxicity

- Human Data
  - An irritant (eyes, skin, mucous membranes)
  - A CNS depressant at high concentrations
  - Produces nausea, vomiting, intragastric discomfort, liver and kidney damage, green-gray urine
- Animal Data
  - Oral LD50 in rats: 2.86 g/kg
  - Induced hyaline droplet-related nephrotoxicity in male rats
  - Green colored urine in rats and guinea pigs
- Genotoxicity
  - Negative in Salmonella mutation assays with or without S-9
  - No increase in micronucleated erythrocytes in peripheral blood in male or female mice

Nomination Rationale

- High production volume and widespread use
- High potential for human inhalation or dermal exposure
- Lack of toxicity and carcinogenicity data
- Structurally similar to decalin and naphthalene (known animal carcinogens)

14-Day Rat Study

- Groups of 5 male and 5 female F344/N rats exposed by inhalation to exposure concentrations of 0, 7.5, 15, 30, 60, and 120 ppm
  - Male NBR rats used as negative control for induction of hyaline droplets
- All F344/N and NBR rats survived
- Body weights of all exposed F344/N rats and NBR rats lower (<10%) relative to controls
- Effects on Kidney:
  - Relative kidney weights increased in males and females
  - Increased α2u-globulin and hyaline droplets in exposed male F344/N rats; none in male NBR rats
  - Dark urine in all exposed rats
- Effects on Nose:
  - Nasal mononuclear cell infiltration in all exposed rats
  - Olfactory epithelium degeneration and necrosis and Bowman's gland hypertrophy in 120 ppm male F344/N rats
- The same exposure concentrations were used in the 90-day study
  - No NBR rats included

90-Day F344/N Rat Study Results

- All rats survived
- Body weights of all exposed groups similar to controls
- Effects on Kidney:
  - Relative kidney weights of 60 and 120 ppm males and females increased
  - Exposure concentration-related increase of hyaline droplet, α2u-globulin, and labeling indices in males but not in females
  - Concentration-related increase in urinary aspartate aminotransferase/creatinine in males and females and lactic dehydrogenase/creatinine in males
  - Dark urine in all male and female groups at >30 ppm
- Effects on Nose:
  - Concentration-related increase in incidence and severity of olfactory epithelium necrosis and regeneration in males and females
- **Exposure concentrations selected for 2-year study: 0, 30, 60, and 120 ppm**

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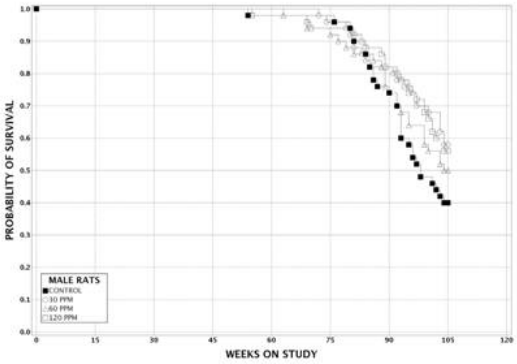
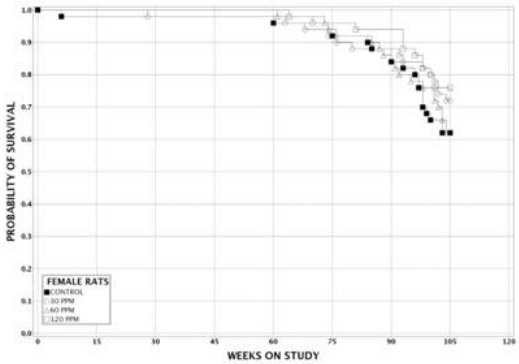
Kaplan-Meier Survival Curves for Rats Exposed to Tetralin by Inhalation for 2 Years





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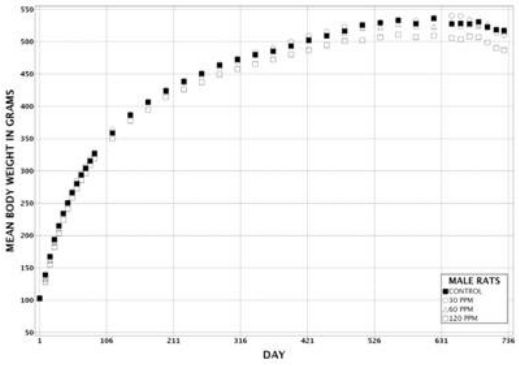
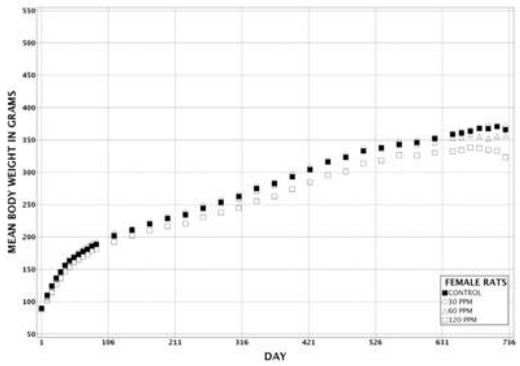
Growth Curves for Rats Exposed to Tetralin by Inhalation for 2 Years





Incidences of Kidney Lesions in the 2-Year Rat Study

Exposure concentration (ppm)	0	30	60	120
Males				
Cortical renal tubule hyperplasia	1	2	1	7*
Pelvis transitional epithelium hyperplasia	1	1	0	7*
Nephropathy (CPN)	48 (2.6)[a]	50 (3.0)	48 (3.0)	50 (3.4)
Renal tubule adenoma	0	3	2	6*
Females				
Nephropathy (CPN)	40	41	44	49*

N=50; *P≤0.05;
[a]Severity of lesions (1=minimal; 2=mild; 3=moderate; 4=marked)

Other Neoplastic and Nonneoplastic Lesions in the 2-Year Rat Study

Exposure concentration (ppm)	0	30	60	120
Males				
Testis germinal epithelium atrophy	32	42*	34	45**
Testis interstitial cell adenoma	29	39*	31	41**
Females				
Hepatocellular adenoma or carcinoma[a]	0	0	1	4
Endometrium, hyperplasia	2 (1.0)[b]	5 (1.2)	7 (1.4)	11** (2.3)
Stromal polyp or stromal sarcoma	6	11	10	17*

N=50; *P≤0.05; **P≤0.01;
[a]Historical control incidence for 2-year inhalation studies: 0/350;
[b]Severity of lesions (1=minimal; 2=mild; 3=moderate; 4=marked)

Nasal Lesions in Male and Female Rats in 2-Year Study

Exposure concentration (ppm)	0	30	60	120
Males				
Glands dilatation	0	3	3	16**
Olfactory epithelium				
Degeneration	1	40**	43**	42**
Hyperplasia, basal cell	0	38**	48**	48**
Inflammation, suppurative	0	12**	8**	10**
Metaplasia	0	17**	31**	37**
Mineralization	0	5*	12**	17**
Respiratory epithelium inflammation, chronic	4	4	18**	16**
Females				
Glands dilatation	0	6	10**	16**
Olfactory epithelium				
Degeneration	0	47**	50**	46**
Hyperplasia, basal cell	0	48**	50**	49**
Inflammation, suppurative	0	16**	15**	19**
Metaplasia	0	41**	43**	49**
Mineralization	0	2	8*	13**
Respiratory epithelium inflammation, chronic	1	7*	11*	12**

N=50; *P≤0.05; **P≤0.01

14-Day and 90-Day Mouse Studies

- 14-Day Study
  - Exposure concentrations: 0, 7.5, 15, 30, 60, and 120 ppm
  - All mice survived
  - Body weights similar in all groups
  - Dark urine
  - Olfactory epithelium atrophy and Bowman's glands hyperplasia and dilation in 120 ppm males and females
- 90-Day Study
  - Exposure concentrations: 0, 7.5, 15, 30, 60, and 120 ppm
  - All mice survived
  - Body weights of 60 and 120 ppm males lower than controls
  - Dark stained urine in all dosed groups

Lesions in the Mouse 90-Day Study

Exposure concentration (ppm)	0	7.5	15	30	60	120
Males						
Olfactory epith. metaplasia	0	0	0	0	9**	10**
Respiratory epith. hyaline droplets	0	0	0	0	0	9**
Urinary transitional epith. granules	0	10**	10**	10**	10**	10**
Females						
Olfactory epith. metaplasia	0	0	0	0	10**	10**
Respiratory epith. hyaline droplets	0	0	0	0	8**	10**
Urinary transitional epith. granules	0	10**	10**	10**	10**	10**
Ovary Atrophy	0	0	0	0	4*	8**
Uterus Atrophy	0	0	2	2	6**	8**

N=10; *P≤0.05; **P≤0.01

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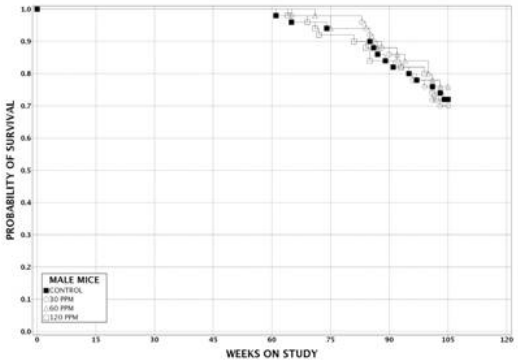
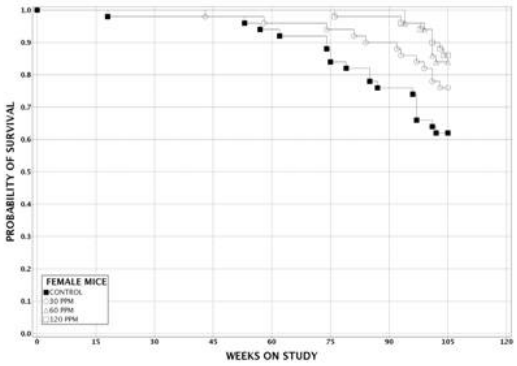
Kaplan-Meier Survival Curves for Mice Exposed to Tetralin by Inhalation for 2 Years





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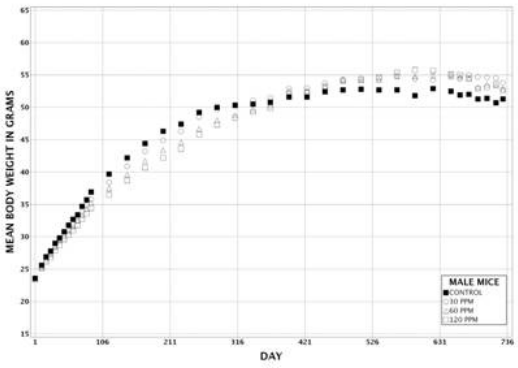
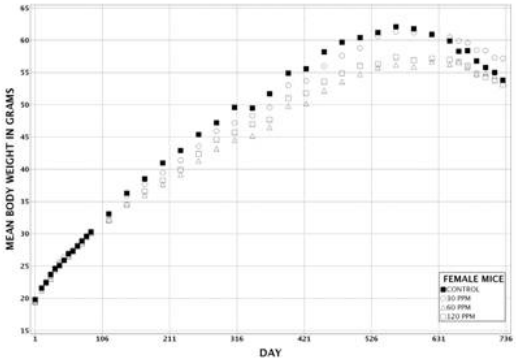
Growth Curves for Mice Exposed to Tetralin by Inhalation for 2 Years





Incidences of Spleen Hemangiosarcoma in the Female Mouse 2-Year Study

Exposure concentration (ppm)	0	30	60	120
Spleen hemangiosarcoma[a]	1	0	1	4

N=50;
[a]Historical control incidence for 2-year inhalation studies: 6/398 (1.5%), range: 0%-4%

Nonneoplastic Lesions in the Mouse 2-year Study

Exposure concentration (ppm)	0	30	60	120
Males				
Nose				
Glands, oflactory epith. hyperplasia	14	49**	50**	49**
Olfactory epith. atrophy	2	49**	50**	50**
Olfactory epith. metaplasia, respiratory	2	47**	50**	49**
Inflammation, suppurative	2	26**	45**	45**
Urinary Bladdar, Transitional Epith. Eosinophilic Granules	0	47**	50**	48**
Females				
Nose				
Glands, oflactory epith. hyperplasia	17	50**	50**	49**
Olfactory epith. atrophy	1	50**	50**	49**
Olfactory epith. metaplasia, respiratory	1	49**	50**	49**
Inflammation, suppurative	3	28**	48**	46**
Urinary Bladdar, Transitional Epith. Eosinophilic Granules	0	50**	49**	49**
Eye, cornea, mineralization	0	3	3	12**

N=50; *P≤0.05; **P≤0.01

Conclusions

- Under the condition of the 2-year inhalation studies, there was:
  - ***some evidence of carcinogenic activity*** of tetralin in male F344/N rats based on the increased incidence of cortical renal tubule adenoma
    - testicular interstitial cell adenoma may have been related to exposure
  - ***some evidence of carcinogenic activity*** of tetralin in female F344/N rats based on the increased incidence of heptocellular neoplasms and uterine stromal polyp
  - ***no evidence of carcinogenic activity*** of tetralin in male B6C3F1 mice
  - ***equivocal evidence of carcinogenic activity*** of tetralin in female B6C3F1 mice based on increased incidence of splenic hemangiosarcoma